

POLICY TITLE	PROGESTERONE THERAPY AS A TECHNIQUE TO REDUCE PRETERM DELIVERY IN HIGH RISK PREGNANCIES
POLICY NUMBER	MP-7.025

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## I. POLICY

For women with a singleton pregnancy and prior history of spontaneous preterm birth before 37 weeks' gestation, the following may be considered **medically necessary**:

- Weekly injections of 17 alpha-hydroxyprogesterone caproate, initiated between 16 and 20 weeks of gestation and continued until 36 weeks 6 days.
- Daily vaginal progesterone between 24 and 34 weeks of gestation

For women with a singleton pregnancy and a short cervix (less than 20 mm), the following may be considered **medically necessary**:

- Daily vaginal progesterone initiated between 20 and 23 weeks 6 days of gestation and continued until 36 weeks 6 days.

Progesterone therapy as a technique to prevent preterm delivery is considered **investigational** in pregnant women with other risk factors for preterm delivery including, but not limited to:

- Twin or multiple gestations
- Prior episode of preterm labor in current pregnancy (i.e., progesterone therapy in conjunction with tocolysis or following successful tocolysis);
- Positive tests for cervicovaginal fetal fibronectin
- Cervical cerclage
- Uterine anomaly

There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with these indications.

### Policy Guidelines

Note: It should be noted that appropriate training of ultrasonographers with ongoing quality assurance programs are considered critical to the accurate measurement of cervical length in the second trimester. In the Hassan et al. 2011 study, all sonographers involved in sonographic

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measurement of cervical length were required to participate in a training program and to obtain certification.

Centers that measure cervical length may need to do an additional ultrasound during pregnancy. The ultrasound takes place between 19 0/7 and 23 6/7 weeks of gestation.

***Cross-reference:***

MP-7.019 Home Uterine Activity Monitor  
MP-7.022 Acute and Maintenance Tocolysis

**II. PRODUCT VARIATIONS****TOP**

*[N] = No product variation, policy applies as stated*

*[Y] = Standard product coverage varies from application of this policy, see below*

[N] Capital Cares 4 Kids

[N] Indemnity

[N] PPO

[N] SpecialCare

[N] HMO

[N] POS

[N] SeniorBlue HMO

[Y] FEP PPO\*

[N] SeniorBlue PPO

\*Refer to FEP Medical Policy Manual MP-4.01.16 Progesterone Therapy as a Technique to Reduce Preterm Birth in High Risk Pregnancies. The FEP Medical Policy manual can be found at: [www.fepblue.org](http://www.fepblue.org)

**III. DESCRIPTION/BACKGROUND****TOP**

Preterm birth is the leading cause of neonatal morbidity and mortality, and effective primary preventive interventions have remained elusive. In recent years, there has been renewed interest in the use of progesterone (injectable and intravaginal formulations) to prevent preterm birth.

Preterm labor and delivery are major determinants of neonatal morbidity and mortality. In the U.S., the rate of preterm birth is 12%. A variety of diagnostic and prophylactic measures have been investigated including home uterine activity monitoring, subcutaneous terbutaline tocolytic therapy, and routine culture and antibiotic treatment of subclinical bacterial vaginosis. To date, none of these had made a significant demonstrable impact on the incidence of preterm delivery. In the past, intramuscular (IM) injections of hydroxyprogesterone caproate (i.e., Delalutin) were used routinely to prevent premature labor. However, the drug was shown to have teratogenic properties, and the U.S. Food and Drug Administration (FDA) labeled the drug

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as Category D (i.e., studies have demonstrated fetal risk, but use of the drug may outweigh the potential risk). Delalutin was voluntarily withdrawn from the market in 1999.

In recent years, there has been renewed research interest in intramuscular injection of 17 alpha-hydroxyprogesterone caproate (17P). 17P is a weakly acting, naturally occurring progesterone metabolite, which when coupled with caproate dextran works as a long-acting progestin when administered intramuscularly. 17P has been manufactured locally by compounding pharmacies. After an extended application process, Makena®, another injectable form of 17P was approved by the FDA in February 2011. Intravaginal progesterone gel and suppositories have also been used.

### **Regulatory Status**

On February 3, 2011, an injectable formulation containing 17-alpha-hydroxyprogesterone caproate was approved by the FDA through the premarket approval process. The product is called Makena and is being marketed by K-V Pharmaceuticals. It is indicated to reduce preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. Makena is not intended for use in women with multiple gestations or in women with other risk factors for preterm birth. Injectable hydroxyprogesterone caproate had previously been approved by the FDA in 1956 under the brand name Delalutin®. This product was voluntarily withdrawn from the market in 1999. As of August 2013, McGuff Pharmaceuticals is pursuing the approval of an Abbreviated New Drug Application (ANDA) for injectable hydroxyprogesterone caproate; this is a generic version of Delalutin.

## **IV. RATIONALE**

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This policy is updated regularly with searches of the MEDLINE database. The most recent literature search was performed for the period July 2012 through July 22, 2013. Following is a summary of the key literature to date.

### **Overall effectiveness of progesterone for reducing preterm birth in high-risk pregnancies**

Several systematic reviews and meta-analyses summarizing data on progesterone therapy to reduce pre-term birth in high-risk pregnancies have been published. Most recently, in 2012, Sotiriadis and colleagues published findings from a meta-analysis of randomized controlled trials (RCTs) comparing progesterone and placebo in women at high risk of preterm birth due to a history of preterm birth, short cervix during the second trimester, or multiple pregnancies. (1) The analysis focused on neonatal and perinatal mortality rates; studies that did not report these outcomes were excluded. Neonatal mortality was defined as the number of deaths from birth to 28 days. Perinatal mortality was defined as deaths that occurred at less than 28 days of age plus fetal deaths that had a stated or presumed period of gestation of 20 weeks or more. Findings were reported separately for singleton, twin and triplet gestations. A total of 6 trials published between 2003 and 2011 provided data for the analysis of singleton pregnancies. Three of the studies used systemic progesterone (oral or intramuscular), and 3 used vaginal

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progesterone. A pooled analysis of data from the studies on singleton pregnancies found a significantly lower risk of neonatal death in the group receiving progesterone versus placebo (relative risk [RR]: 0.49, 95% confidence interval [CI]: 0.29 to 0.82). No significant difference between groups was found for the outcome of perinatal death. A significant benefit for progesterone was also found for a composite adverse outcomes variable (RR: 0.58, 95% CI: 0.37-0.89). The analyses on studies evaluating twin and triplet pregnancies are discussed in the sections below on these topics.

Previously, in 2009, Rode and colleagues published a meta-analysis of 6 studies on progesterone therapy for women with singleton pregnancies. (2) The primary outcomes were preterm birth prior to 37 weeks' gestation and preterm birth prior to 32 weeks' gestation. Five trials reported the rate of preterm birth prior to 37 weeks' gestation. A pooled analysis of data from these studies found a statistically significant benefit of progesterone treatment compared to placebo (RR: 0.77, 95% CI: 0.67-0.87). A pooled analysis of data from 3 studies on preterm birth prior to 32 weeks' gestation also found that progesterone was beneficial (RR: 0.61, 95% CI: 0.45-0.82). Five studies provided data on perinatal death. A pooled analysis found a significant reduction in the rate of perinatal death with progesterone therapy compared to placebo (RR: 0.54, 95% CI: 0.31-0.93). The 2009 Rode study was an update of a 2006 Cochrane review. (3) At the time of the Cochrane review, 4 RCTs evaluating progesterone therapy given to women with a history of a preterm birth or other high-risk factors had been published.

### **History of prior spontaneous preterm birth**

RCTs focusing on women with singleton pregnancies and a history of previous preterm birth are described below:

#### *Intramuscular progesterone*

One trial using intramuscular progesterone and including women with a singleton pregnancy and a history of previous spontaneous birth has been published. (Note: This is the trial upon which FDA approval of an injectable formulation of 17P in 2011 was based). In 2003, Meis and colleagues published findings of a study in which 463 women were randomized to receive either weekly intramuscular injections of 17P or a placebo injection. (4) Injections began at 16 to 20 weeks of gestation and continued until 36 weeks of gestation. The frequency of delivery before 37 weeks' gestation, the primary outcome, was 36.3% in the progesterone group, as compared with 54.9% in the placebo group. While this difference is statistically significant ( $p<0.001$ ), it is important to note that the rate of preterm delivery in the placebo group (54.9%) is exceptionally high. The authors acknowledge the high incidence of preterm delivery in the control group and suggest that this rate may be related to the overall high risk in the enrolled patients. For example, the mean gestational age of the prior preterm delivery in the placebo group was 31 weeks  $\pm$  4.2 weeks. As noted by the authors, the risk of preterm delivery increases with a decreasing gestational age of the prior preterm delivery. The frequency of delivery before 35 weeks was 20.6% in the progesterone group and 30.7% in the placebo group; this difference was also statistically significant ( $p<0.02$ ). While the high incidence of preterm

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delivery in the control group of the Meis et al. trial is unexplained, the study is otherwise well-designed and does report that intramuscular 17P administration is associated with a statistically significant reduction in preterm delivery. In 2007, follow-up data on children born during the Meis et al. trial of 17P were published. (5) Of the 429 infants discharged alive after birth, 278 (65%) were enrolled. Loss to follow-up occurred due to the loss of centers that were no longer in the network (n=81) and parents or guardians who were not able to be contacted (n=55) or who declined to participate (n=15). There was a 2:1 treatment ratio in the original study, resulting in the follow-up of 194 children from the 17P group and 84 from the control group. An average 48 months of follow-up (from <36 to 60 months) found no differences in physical measures, diagnoses given by health professionals, or in the caregiver's assessment of the health of the children.

#### *Vaginal progesterone*

Three randomized trials evaluated vaginal progesterone for women with singleton pregnancies in which at least 90% of the population had a history of previous preterm birth.

In 2003, Da Fonseca and colleagues in Brazil reported the results of a trial that randomized 157 women with singleton pregnancies considered at high risk for preterm delivery to receive either daily progesterone or placebo suppositories. (6) Inclusion criteria included either a prior spontaneous preterm birth or other risk factors. A total of 142 of 157 (90%) of patients completed the study. Of these, 133 (93.7%) had a previous preterm birth, 5 (3.5%) had uterine malformation, and 4 (2.8%) had an incompetent cervix. The mean gestational age of the prior preterm birth was 33 weeks. The rate of delivery before 37 weeks was 13.8% in the intervention group and 28.5% in the control group. This difference was statistically significant,  $p<0.03$ . The rate of delivery before 34 weeks was 2.8% in the intervention group and 18.6% in the placebo group; this was also statistically significant in favor of the progesterone treatment group,  $p<0.002$ .

A large multinational study (including sites in the U.S.) was published in 2007 by O'Brien and colleagues. (7) The study randomized 659 women with a singleton pregnancy to once-daily treatment with progesterone vaginal gel or placebo between 18 and 37 weeks' gestation. Results from 611 women (93%) showed no difference between the active and control groups for rate of preterm birth at 37 weeks or less (42% vs. 41%), rate of preterm birth at 32 weeks or less (10% vs. 11%), mean gestational age at delivery (36.6 weeks vs. 36.6 weeks – all respectively), or any other maternal or neonatal outcome measures. Compliance and adverse events were similar for the two groups.

In 2009, Majhi and colleagues in India published a study including 100 women with singleton pregnancies and a history of prior spontaneous preterm birth. (8) Women were randomized to receive micronized natural progesterone intravaginally via capsules (n=50) or no treatment (n=50). All participants were included in the analysis; there was no loss to follow-up. Six of 50 (6%) in the progesterone group and 19 of 50 (38%) in the control group had a preterm birth before 37 weeks; this difference was statistically significant,  $p=0.003$ . The difference in the rate

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of preterm birth before 34 weeks, 2 (4%) in the progesterone group and 3 (6%) in the control group, was not statistically significant ( $p=0.64$ ), but this analysis may have been underpowered.

An unresolved issue is whether efficacy differs by the type of formulation of the intravaginal progesterone. The O'Brien et al. study, which had negative findings, used vaginal gel while the Da Fonseca and Majhi et al. studies, both of which had positive findings, used suppositories. (In the Majhi study, capsules were used).

#### *Intramuscular versus vaginal progesterone*

An unblinded RCT, published in 2012 by Mahar and colleagues, compared the safety and efficacy of vaginal and intramuscular progesterone for reducing the rate of preterm birth in women with singleton pregnancies and a prior history of preterm birth. (9) The study was conducted at a single center in Saudi Arabia and no industry support was reported. Participants were at a gestational age between 14 and 18 weeks, and the primary efficacy outcome was delivery before 34 weeks' gestation. A total of 518 women were randomized to receive intramuscular progesterone (n=256) or vaginal progesterone gel (n=262). A total of 16 participants were lost to follow-up. There were 42 deliveries before 34 weeks in the vaginal progesterone group (17%) and 64 deliveries before 34 weeks in the intramuscular progesterone group (26%). The difference between groups was statistically significant, favoring the vaginal progesterone group (odds ratio [OR]: 0.58, 95% CI: 0.37 to 0.89). Secondary maternal outcomes, including admission for threatened preterm labor, premature rupture of membranes and use of tocolytic therapy, did not differ significantly between groups. Most secondary neonatal outcomes, including rates of neonatal death, respiratory distress syndrome and sepsis did not differ significantly between groups. The exception was admission to the neonatal intensive care unit; there was a significantly higher rate in the intramuscular progesterone group (n=64, 26%) than the vaginal progesterone group (n=39, 15%),  $p=0.006$ . A significantly higher rate of adverse effects were reported by patients in the intramuscular progesterone group (n=35, 14%) than the vaginal progesterone group (n=19, 8%),  $p=0.017$ .

**Section summary:** In women with singleton pregnancies and a history of preterm birth, one RCT found that 17P was associated with a statistically significant reduction in the rate of preterm delivery. Three RCTs have evaluated vaginal progesterone for reducing preterm delivery in this same population of women. Two out of 3 of the studies found that vaginal progesterone was associated with a reduction in preterm delivery before 37 weeks' gestation. The third study found no significant benefit of vaginal progesterone. The two positive studies used vaginal suppositories and the negative study used vaginal gel. There is inconclusive evidence to determine whether one formulation of vaginal progesterone may be more effective than another. One RCT found lower rates of preterm delivery in women receiving vaginal gel compared to intramuscular progesterone and a higher rate of adverse effects in the intramuscular progesterone group. This one study, conducted at a single center outside of the U.S., is insufficient for drawing conclusions about the relative efficacy of intramuscular versus vaginal progesterone.

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### Short cervical length

#### *Intramuscular progesterone*

One RCT, by Berghella and colleagues, included a planned secondary analysis of preterm birth in women with a short cervical length (less than 25 mm at 16-22 weeks' gestation) and history of prior preterm birth. (10) The study was primarily intended to evaluate the efficacy of cerclage, but study participants were stratified at randomization to use or not use 17P, so the additional impact of 17P on outcomes could be examined. The 17P group did not have lower preterm birth rates, either in the group assigned to cerclage or the group assigned to no cerclage. However, in the no cerclage group, perinatal death occurred in 2 (4%) cases in the group that used 17P, and 23 (23%) cases in the group that did not use 17P; this difference was statistically significant ( $p=0.003$ ). Moreover, birth before 24 weeks occurred in one (2%) pregnancy in the 17P group and 20 (20%) in the no 17P group ( $p=0.002$ ). A limitation of this analysis is that the number of women who used 17P and did not receive cerclage was small. Moreover, all women in the study had a history of previous spontaneous preterm birth, so the study does not provide data on the efficacy of 17P for women with a short cervical length but without a prior preterm birth.

A 2012 double-blind RCT by Grobman and colleagues evaluated the efficacy of intramuscular 17P for preventing preterm birth in women with short cervical length and who were nulliparous, i.e., participants did not have a history of prior preterm birth. (11) The study was conducted at 14 centers in the U.S. Short cervix was defined as <30 mm between 16 weeks 0 days and 22 weeks 3 days. A total of 657 women were randomized to weekly injections of 17P ( $n=327$ ) or placebo injections ( $n=330$ ). No participants were lost to follow-up. The primary outcome, preterm birth before 37 weeks, occurred in 82 women in the 17P group (25%) and 80 women in the placebo group (24%). The difference between groups was not statistically significant (RR: 1.03, 95% CI: 0.79 to 1.35). Other outcomes, including delivery before 35 weeks, gestational age at delivery, hospital visits for preterm labor and side effects, also did not differ significantly between groups. The investigators initially planned to enroll 500 women in each group, but an interim analysis by an independent data and safety monitoring board determined that there was an extremely low probability of finding a significant difference between groups if enrollment continued and therefore the trial was halted early.

#### *Vaginal progesterone*

Several RCTs and a meta-analysis of RCTs have been published. In 2012, Romero and colleagues published a metaanalysis of individual patient data from RCTs comparing vaginal progesterone to placebo or no treatment in asymptomatic pregnant women with a sonographic short cervix (cervical length 25 mm or less) in the mid-trimester. (12) A total of 5 RCTs were included in the meta-analysis. Two of the trials [discussed below (13, 14)] limited enrollment to women with a short cervix and the others included women with a wider range of risk factors but reported results separately for women with a short cervix. All of the studies were double-blind and placebo-controlled. The studies included data on a total of 775 women, 723 (93%) with singleton pregnancies and 52 (7%) with twin pregnancies. A pooled analysis of data from the 5

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studies found that treatment with vaginal progesterone was associated with a statistically significant reduction in the risk of preterm birth before 33 weeks' gestation compared to placebo (12.4% vs. 22.0%, respectively; RR: 0.58, 95% CI: 0.42 to 0.80). When the analysis was limited to women with a singleton birth and no history of previous preterm birth, there remained a significant benefit of progesterone treatment to reduce the rate of preterm birth before 33 weeks' (RR: 0.60, 95% CI: 0.39 to 0.92).

The Romero et al. study also examined the preterm birth outcome for other time periods. In the analysis of all available data, rates of preterm birth before 35, 34, 30 and 28 weeks' gestation were significantly lower in the group receiving vaginal progesterone compared to placebo. The outcome of preterm birth before 36 weeks' gestation was marginally significant, and there was not a significant difference between groups in the rate of preterm birth before 37 weeks' gestation (37% in the treatment group and 43% in the placebo group).

Following are brief descriptions of the 2 RCTs that had the primary aim of evaluating vaginal progesterone for treating women at high-risk of preterm delivery due to short cervical length.

In 2007, Fonseca and colleagues randomized 250 women with a cervical length of 15 mm or less to nightly (between 24 and 34 weeks of gestation) vaginal progesterone or placebo capsules. (13) Cervical length was measured at the time of routine ultrasound between 20 and 25 weeks' gestation. Spontaneous preterm delivery before 34 gestational weeks' gestation occurred in 24 (19%) women in the progesterone group and 43 (34%) in the control group,  $p=0.007$ . Similarly, there were significantly more deliveries of any type before 34 weeks in women who received placebo (45, 36%) compared to progesterone (26, 21%),  $p=0.008$ . Other outcomes, including neonatal death and birth weight, did not differ significantly between groups.

In 2011, Hassan and colleagues published a double-blind, placebo-controlled, RCT with asymptomatic women with singleton pregnancies who had a short cervix (the PREGNANT trial). (14) The study was conducted at 44 centers in 10 countries, including the United States. Women between 19 weeks 0 days and 23 weeks 6 days were eligible for screening. Short cervix was defined as between 10-20 mm. A total of 32,091 women underwent sonographic measurement of cervical length, and 733 (2.3%) were found to have cervical length between 10-20 mm. Of these, 465 (63%) agreed to participate in the study. Seven women were lost to follow-up, and 458 women were included in the intention-to-treat analysis group. Of these, 235 were assigned to the progesterone group and 223 to the placebo group. Seventy-two of 458 women (16%) had a history of previous preterm birth before 35 weeks' gestation. The primary outcome was birth before 33 weeks' gestation. In the intention-to-treat population (all randomized women), this occurred in 21 patients (8.9%) in the vaginal progesterone group and 36 (16.1%) in the placebo group (RR: 0.55, 95% CI: 0.33 to 0.92,  $p=0.02$ ). The vaginal progesterone group also had significantly lower rates of secondary outcomes than the placebo group including preterm birth before 28 weeks (5.1% vs. 10.3%,  $p=0.04$ ) and a composite neonatal morbidity or mortality variable (3.0% vs. 7.6%,  $p=0.04$  – both respectively).

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Respiratory distress syndrome occurred in 7 of 235 (3%) infants in the progesterone group and 17 of 223 (7.6%) infants in the placebo group,  $p=0.026$ .

The authors also conducted a prespecified analysis of 387 compliant patients, which excluded those who were less than 80% compliant with treatments ( $n=52$ ), had no documented delivery date ( $n=4$ ), or had a cerclage ( $n=17$ ). In the compliant group, there was also a significantly lower rate of preterm delivery before 33 weeks in the group assigned to vaginal progesterone (11 of 194, 5.7%) than the placebo group (25 of 193, 13%),  $p=0.01$ . The rate of preterm delivery before 28 weeks' gestation and 35 weeks' gestation also favored the vaginal progesterone group, but there was no significant difference in the rate of preterm delivery before 37 weeks' gestation. There was not a significant difference between groups in the combined neonatal morbidity and mortality variable (11, 5.7% in the progesterone group and 21, 10.9% in the placebo group, unadjusted  $p$ -value=0.06).

The authors noted that the precise mechanism by which progesterone may prevent preterm labor in women with a short cervix is unknown but that a local effect is likely. They also described several differences between this study and the 2007 Fonseca et al. study; in this study, twin gestations, which have not been shown to benefit from progesterone were excluded, and treatment was initiated as early as 20 weeks' of gestation, while the Fonseca study began at 24 weeks, and the cervical length was 10 to 20 mm rather than less than 15 mm. Patients with a cervical length of 10 mm or less are known to have a higher rate of intra-amniotic infection and inflammation, and therefore are less likely to benefit from progesterone treatment than women with a longer cervix. The authors stated that optimal treatment of women with cervical length less than 10 mm has not been established.

**Section summary:** Two RCTs focused on the evaluation of vaginal progesterone for preventing preterm birth in women with short cervical length; several other RCTs on vaginal progesterone have reported data on this group of women. A recent meta-analysis of data from 5 RCTs found that vaginal progesterone significantly reduces the rate of preterm delivery in women with a short cervical length. In addition, there was benefit in the subgroup of women with a singleton pregnancy and no prior history of preterm birth. There is insufficient evidence from 2 RCTs that injectable progesterone is effective for preventing preterm birth in women with short cervical length.

### **Twin gestations**

The 2012 Sotiriadis meta-analysis, described above, included a pooled analysis of studies evaluating progesterone to reduce perinatal mortality in twin gestations. (1) Seven trials were identified on twin pregnancies. Pooled analyses found that administration of progesterone did not significantly affect the rate of neonatal death and that the risk of perinatal death was significantly higher compared to placebo (RR: 1.55, 95% CI: 1.01 to 2.73. In addition, there were significantly more adverse events (composite variable) in the group receiving progesterone compared to placebo (RR: 1.21, 95% CI: 1.10 to 1.43).

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The largest RCT on twin pregnancies published to date, and also the study with the longest follow-up, was published in 2011 by Rode and colleagues (the PREDICT trial). (15) The study was conducted in Denmark and Austria. A total of 667 pregnant women with twins were randomized to receive vaginal progesterone or placebo. Treatment was initiated between 20 weeks' gestation up until 24 weeks' gestation and continued until either 34 weeks' gestation, rupture of the membranes, or delivery. The primary outcome, delivery before 34 weeks' gestation did not differ significantly between groups. Preterm delivery before 34 weeks occurred in 51/334 (15.3%) of women in the treatment group and 63/341 (18.5%) of women in the control group (OR: 0.8, 85% CI: 0.5 to 1.2). Similarly, there were no significant differences between groups in the rate of preterm delivery before 22, 28, 32 or 37 weeks' gestation. Rates of neonatal outcomes e.g., birthweight, neonatal death, perinatal complications, also did not differ significantly between groups. The investigators conducted follow-ups 6 and 18 months after birth. They did not find significant differences between groups on children's scores on the Ages and Stages Questionnaire (ASQ), a parent-administered instrument.

Another large RCT was published in 2007 by Rouse and colleagues. (16) In this trial, 661 women with twin gestations were randomized to receive weekly (from 16 to 35 weeks' gestation) intramuscular injections of 17P or placebo. No differences were observed in the occurrence of delivery or fetal death before 35 weeks (42% vs. 37%) or in serious adverse fetal or neonatal events (20% vs. 18%, both respectively).

Moreover, in 2010, Norman and colleagues published findings from a prevention of preterm birth in twin pregnancy trial (STOPPIT) that was conducted in the U.K. (17) This double-blind study randomized 500 women with twin pregnancies to either daily progesterone gel or placebo gel administered vaginally starting at 24 weeks' gestation. Three women in each group were lost to follow-up, leaving 247 per group in the analysis. The primary outcome, delivery or intrauterine death before 34 weeks, did not differ significantly between groups. The outcome was attained by 61 of 247 (24.7%) in the progesterone group and 48 of 247 (19.6%) in the placebo group (OR: 1.36; 95% CI: 0.89-2.09). The secondary outcomes, gestational age at birth; admission to the neonatal care unit; and duration of stay in the neonatal care unit, also did not differ significantly between groups.

Similarly, subsequent RCTs, published in 2012 and 2013, did not find that progesterone therapy was effective for preventing premature birth in women pregnant with twins. (18-20)

**Section summary:** Numerous RCTs and a meta-analysis have consistently found that progesterone is not associated with decreased rates of preterm delivery in pregnant women with twins. In the individual RCTs, there was no statistically significant effect of progesterone on beneficial neonatal outcomes; in addition, the metaanalysis found that progesterone was associated with a higher rate of perinatal death.

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### Triplet gestations

The 2012 Sotiriadis metaanalysis (1) identified 2 trials on progesterone in women with triplet gestations. Pooled analyses of data from these 2 studies did not find any statistically significant differences in outcomes between women receiving progesterone or placebo.

Both of the trials evaluated intramuscular injections of 17P. Caritis and colleagues randomized healthy women with triplets to receive weekly intramuscular injections of either 17P or placebo starting at 16 to 20 weeks and ending at delivery or 35 weeks of gestation. (21) The primary study outcome was delivery or fetal loss before 35 weeks. A total of 134 women were randomized, with 71 assigned to 17 alpha-hydroxyprogesterone caproate and 63 to placebo; none were lost to follow-up. The proportion of women experiencing the primary outcome (a composite of delivery or fetal loss before 35 weeks) was similar in the 2 treatment groups: 83% of pregnancies in the 17 alpha-hydroxyprogesterone caproate group and 84% in the placebo group (relative risk: 1.0). The other trial was published in 2010 by Combs and colleagues. (22) A total of 81 women were included, 56 assigned to receive intramuscular injections of 17P and 25 to placebo. Treatment started at 16-22 weeks' gestational age and continued until 34 weeks. There was not a significant difference in the mean gestational age at delivery (31.9 in the 17P group and 31.8 in the placebo group,  $p=0.36$ ). However, there were 13 mid-trimester fetal losses in the 17P group and none in the placebo group,  $p<0.02$ .

Section summary: Two RCTs and a meta-analysis of data from these 2 trials did not find that progesterone was associated with improved outcomes in women pregnant with triplets.

### Preterm rupture of the membranes (PPROM)

In 2010, Briery and colleagues published a study including women with singleton pregnancies diagnosed with preterm rupture of the membranes (PPROM) at 20-30 weeks' gestation. (23) They were randomized to receive weekly injections of 17-alpha-hydroxyprogesterone ( $n=33$ ) or placebo ( $n=36$ ). Two women did not finish the study; however, data were analyzed on an intention-to-treat basis. There was no significant difference between groups in the gestational age at delivery (a mean of 27.3 weeks in the progesterone group and 29.5 weeks in the placebo group,  $p=0.15$ ). Neonatal outcomes including birth weight, length of stay in the neonatal intensive care unit, and neonatal morbidity and mortality, also did not differ significantly between groups. For example, mean birth weight was 1,216 grams in the progesterone group and 1,396 grams in the placebo group,  $p=0.15$ .

Conclusion: The single published RCT identified did not find that outcomes were improved in women with singleton pregnancies experiencing PPROM who received progesterone versus placebo.

### Prevention of preterm delivery after successful tocolysis for preterm labor

Three published RCTs have addressed use of progesterone therapy for reducing preterm birth in women after successful tocolysis. All 3 trials included a usual care comparison group; that is, studies were not placebo-controlled. A 2012 trial by Saleh Gargari and colleagues in Iran included 72 women pregnant with singletons who had undergone successful tocolysis with

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magnesium sulfate for preterm labor. (24) After tocolysis, participants were randomly assigned to apply vaginal progesterone suppository until delivery or usual care. The authors stated that study personnel (other than statisticians) and participants were blinded to treatment group; however, the ability to blind a no-treatment control group may be limited. The study evaluated numerous outcomes, and there was no primary outcome specified. Two main delivery-related outcomes were reported. The mean gestational age at delivery was 36.2 weeks (standard deviation [SD]: 1.4) in the progesterone group and 34.1 (SD: 1.5) in the usual care group; p=0.039. The mean length of time that delivery was postponed was 4.0 weeks (SD: 1.5) in the progesterone group and 1.4 weeks (SD: 0.2) in the usual care group, p=0.048. If the p value had been adjusted to account for 2 comparisons (i.e., p<0.025 instead of p<0.05), it is unlikely that the differences in these outcomes would have been statistically significant. The number of neonatal deaths was 3 (4.2%) in the progesterone group and 8 (11%) in the usual care group; the difference between groups was not statistically significant, p=0.08, but the study likely was underpowered to detect differences between groups in the rate of neonatal death given the low number of deaths overall. The number of low birthweight babies was 8 (11%) in the progesterone group and 26 (36%) in the usual care group, p<0.001.

A 2012 open-label multicenter RCT by Rozenberg and colleagues in France evaluated intramuscular progesterone to prevent preterm delivery in 188 pregnant women after a previous episode of successful tocolysis during the same pregnancy. (25) Women had all been admitted for preterm labor with intact membranes. To be eligible for study participation, women also needed to be carrying a singleton pregnancy and to be between the 24<sup>th</sup> and 31<sup>st</sup> week of gestation. Following acute tocolysis, women assigned to progesterone treatment (n=94) received injections of 17P twice a week until 36 weeks' gestation or preterm delivery. Women in the control group (n=94) received usual care. Outcome data were available for 184 of 188 (97%) of participants. An intention-to-treat analysis did not find a statistically significant difference between groups in the study's primary efficacy outcome, time to delivery (from randomization). The time to delivery was a median of 64 days in the 17P group and 67 days in the control group. Other delivery-related outcomes i.e. delivery before 32, 34 and 37 weeks' gestation did not differ significantly between groups. In addition, fetal and neonatal outcomes, including birthweight, rate of neonatal death and rates of respiratory distress syndrome, were not different in the 17P and control groups.

A 2011 RCT by Arikan and colleagues in Turkey compared vaginal progesterone in conjunction with tocolysis to tocolysis-only in 83 pregnant women with symptoms of preterm labor. (26) To be eligible for the study, women needed to be carrying singleton pregnancies, be between 24 and 34 weeks' gestation and be admitted for premature labor with intact membranes, have cervical dilation no more than 2 cm and have no previous cervical cerclage. Women assigned to the treatment group (n=43) received acute tocolysis with ritodrine, followed by intravaginal progesterone. Progesterone use continued until 35 weeks' 6 days gestation or delivery. Women in the control group (n=40) received acute tocolysis and no intravaginal progesterone. In addition, all women received 2 injections of betamethasone. All participants completed the study. A total of 20 (50%) women in the progesterone group and 28

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(65%) of women in the control group experienced preterm delivery before 37 weeks'; the difference between groups was not statistically significant. However, the time from treatment to delivery was significantly longer in the progesterone group (mean of 32.1 days; SD: 17.8 days) than the control group (mean of 21.2 days; SD: 16.3 days),  $p<0.05$ . In addition, the birthweight was significantly higher in the progesterone group (mean 2,983 g) than the control group (mean 2,585 g),  $p<0.05$ . Rates of other neonatal outcomes e.g., mortality, sepsis, respiratory distress syndrome, did not differ significantly between groups. The authors did not report exact  $p$  values, and some may have been close to their cutoff of  $p<0.05$ . Data reporting is insufficient to determine whether  $p$ - values would have been significant if the authors had adjusted for multiple comparisons in their outcomes.

**Section summary:** To date, 3 published RCTs were identified that evaluated progesterone for women with preterm labor. The studies differed in the type and timing of progesterone. No studies used a placebo control group, and only 1 stated that it was double-blind. Neither of the 2 studies that measured the rate of preterm delivery before 37 weeks reported a decrease in the groups receiving progesterone. The third study found a significant benefit of vaginal progesterone in terms of delaying delivery, but  $p$  values were close to the cutoff of 0.05, and neither of the 2 main outcomes was adjusted for multiple comparisons. Two studies found some statistically significant benefits of progesterone therapy e.g., higher birthweight. Due to the limitations and inconsistencies in these RCTs, it is not possible to draw conclusions about the effect of progesterone therapy on health outcomes in women following successful tocolysis for premature labor.

### Ongoing Clinical Trials

A search of the [clinicaltrials.gov](http://clinicaltrials.gov) database in August 2013 identified a number of ongoing trials evaluating progesterone therapy for prevention of preterm birth. The most relevant studies are described below:

Confirmatory Study of 17P Versus Vehicle for the Prevention of Preterm Birth in Women With a Previous Singleton Spontaneous Preterm Delivery (NCT01004029) (27): This RCT is enrolling pregnant women with a history of previous singleton spontaneous delivery. Participants will be randomly assigned to receive injections of 17P or placebo injections. Expected enrollment is 1,707 women. The expected date of study completion is December 2016.

Progesterone for the Management of Preterm, Premature Rupture of the Membranes: A Randomized Controlled Trial (NCT01050647) (28): This RCT is comparing 17P injections to castor oil (placebo) injections in women pregnant with singletons who are diagnosed with PPROM. Expected enrollment is 40 women. The expected date of study completion is August 2014.

Progesterone (17P, Makena®) for Prolongation of Pregnancy in Women With Preterm Rupture of the Membranes (PROM) (17PinPROM) (NCT01119963) (29): This double-blind study includes women with singleton pregnancies diagnosed with PPROM. They will be randomized

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to receive injections of 17P or castor oil (placebo) injections. The expected enrollment is 222 women and the expected date of study completion is January 2014.

Vaginal Progesterone for Prevention of Preterm Birth After an Episode of Preterm Labor (NCT01523483) (30): This RCT is comparing suppositories of vaginal micronized progesterone to placebo for preventing preterm birth in women with singleton pregnancies who have had an episode of preterm birth that responded to tocolytic therapy. Expected enrollment is 60 women. The expected date of study completion is June 2014.

#### **Clinical Input through Specialty Societies and Academic Medical Centers**

In response to requests, input was received through physician specialty societies and academic medical centers while this policy was under review in 2009 and 2011. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. In 2009, the 2 physician specialty societies and 4 academic medical centers, that responded strongly, agreed with the policy statements as adopted in October of that year. There was unanimous agreement that injectable progesterone and vaginal progesterone may be considered medically necessary for women with a singleton pregnancy and a prior history of preterm delivery before 37 weeks' gestation. All but one response indicated there was no evidence supporting one mode of progesterone administration over another. The single response, from an academic medical center, that said there was a difference commented that the Meis and da Fonseca studies differed, and thus one formulation may be preferred over another for a particular patient. The least agreement was regarding short cervical length as a risk factor; however, a majority of those providing input agreed with the current policy statement. The clinical input also raised questions about the clinical applications for cervical length measurement.

In 2011, responses were received from 1 physician specialty society and 6 academic medical centers. There was unanimous agreement among the academic medical center respondents that both weekly injections of progesterone and daily intravaginal progesterone may be considered medically necessary to prevent preterm births in singleton pregnancies when there is a prior history of spontaneous preterm birth. The physician specialty society respondent referred to their organization's clinical guideline which states that progesterone is recommended for women with a history of prior spontaneous preterm birth and that the optimal formulation is not known. Two physician respondents commented that it may be appropriate to begin vaginal progesterone earlier in pregnancy, similar to intramuscular progesterone, which is given starting between 16 and 36 weeks of gestation. One respondent commented that, while data support the use of both intramuscular and vaginal progesterone in women with a history of prior preterm birth, the data are stronger in support of intramuscular progesterone.

There was near-consensus from academic medical center respondents that progesterone therapy may be considered medically necessary for women with a short cervix. The Hassan et al.

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randomized trial was not published at the time clinical input was obtained. The input did not specify timing of vaginal progesterone in women with a short cervix.

Input was also received from 4 academic medical centers on start and stop dates. All of the reviewers supported the use of different start and stop dates, rather than one uniform set of dates across all formulations and indications. The majority of reviewers agreed with all of the recommended start and stop dates as written in the policy statement. For injectable progesterone, the reviewers agreed with using the FDA-approved start and stop dates.

### **Summary**

There is sufficient evidence from randomized controlled trials (RCTs) and meta-analyses of RCTs that injectable and vaginal progesterone are associated with improved health outcomes in women with singleton pregnancies who have a history of prior preterm birth. In addition, there is sufficient evidence that progesterone improves health outcomes in women with singleton pregnancies and short cervical length. Thus, progesterone therapy may be considered medically necessary in the above situations for selected women who meet clinical criteria.

The evidence is insufficient that progesterone is effective for reducing preterm delivery in other situations such as women with twin or multiple gestations, women with preterm rupture of the membranes, or women with a prior episode of preterm labor in the current pregnancy (in conjunction with or following tocolysis) and thus these indications are considered investigational.

### **Practice Guidelines and Position Statements**

A 2012 clinical guideline by the Society for Maternal-Fetal Medicine included the following conclusions and recommendations: (31)

“1. There is insufficient evidence to recommend the use of progestogens in singleton gestations with no prior PTB, and unknown CL.”

“2. In women with singleton gestations, no prior SPTB [spontaneous preterm birth], and short TVU CL 20mm at 24 weeks, vaginal progesterone, either 90-mg gel or 200-mg suppository, is associated with reduction in PTB and perinatal morbidity and mortality, and can be offered in these cases.”

“3. The issue of universal TVU CL screening of singleton gestations without prior PTB for the prevention of PTB remains an object of debate. CL screening in singleton gestations without prior PTB cannot yet be universally mandated. Nonetheless, implementation of such a screening strategy can be viewed as reasonable, and can be considered by individual practitioners. Given the impact on prenatal care and potential misuse of universal screening, stretching the criteria and management beyond those tested in RCTs should be prevented. Practitioners who decide to implement universal TVU CL screening should follow strict guidelines. Practitioners who choose to screen low-risk singleton gestations may consider offering vaginal progesterone, either 90-mg gel or 200-mg suppositories, for short TVU CL 20 mm at 24 weeks.”

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“4. In singleton gestations with prior SPTB 20-36 6/7 weeks, 17P 250 mg IM weekly preferably starting at 16-20 weeks until 36 weeks is recommended. In these women, if the TVU CL shortens to 25mm at 24 weeks, cervical cerclage may be offered.”

“5. Progestogens have not been associated with prevention of PTB in multiple gestations, PTL, or PPROM. There is insufficient evidence to recommend the use of progestogens in women with any of these risk factors, with or without a short CL. Some experts offer 17P to women with a prior SPTB and a current multiple gestation, but there are insufficient data to evaluate the risks and benefits of this intervention in this population.”

Abbreviations used: PTB: preterm birth; SPTB: spontaneous preterm birth; CL: cervical length; TVU: transvaginal ultrasound

In October 2012, the American College of Obstetricians and Gynecologists (ACOG) published a Practice Bulletin on prediction and prevention of preterm birth. (32) The bulletin includes the following recommendations related to progesterone therapy:

- A woman with a singleton pregnancy and a prior spontaneous singleton birth should be offered progesterone supplementation starting at 16-24 weeks of gestation to reduce the risk of recurrent spontaneous preterm birth.
- A woman with a short cervix identified with transvaginal ultrasonography, a singleton gestation and no prior spontaneous preterm birth should be offered vaginal progesterone supplementation if cervical length is 20 mm or less before or at 24 weeks of gestation.
- Progesterone supplementation is not recommended to reduce preterm birth in women with twin or triplet gestations

**V. DEFINITIONS**[\*\*TOP\*\*](#)

**SINGLETON** - refers to one of something described, especially a single infant rather than a twin.

**TOCOLYTIC DRUG** refers to any drug used to suppress premature labor.

**VI. BENEFIT VARIATIONS**[\*\*TOP\*\*](#)

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital for benefit information.

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**VII. DISCLAIMER**[TOP](#)

*Capital's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.*

**VIII. CODING INFORMATION**[TOP](#)

**Note:** This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

**Covered when medically necessary:**

<b>CPT Codes®</b>								
96372	99506							

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<b>HCPCS Code</b>	<b>Description</b>
J1725	INJECTION, HYDROXYPROGESTERONE CAPROATE, 1 MG
J3490	UNCLASSIFIED DRUGS
S9208	HOME MANAGEMENT OF PRETERM LABOR PER DIEM

<b>ICD-9-CM Diagnosis Code*</b>	<b>Description</b>
622.5	INCOMPETENCE OF CERVIX
644.13	OTHER THREATENED LABOR, ANTEPARTUM
649.70	CERVICAL SHORTENING

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<b>ICD-9-CM Diagnosis Code*</b>	<b>Description</b>
654.6	OTHER CONGENITAL OR ACQUIRED ABNORMALITY OF CERVIX
752.43	CERVICAL AGENESIS
V23.41	SUPERVISION OF PREGNANCY WITH HISTORY OF PRE-TERM LABOR

\*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

**The following ICD-10 diagnosis codes will be effective October 1, 2014:**

<b>ICD-10-CM Diagnosis Code*</b>	<b>Description</b>
O09.211- O09.219	Supervision of pregnancy with history of pre-term labor, code range

\*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

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#### X. POLICY HISTORY

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<b>MP 7.025</b>	<b>CAC 4/27/04</b>
	<b>CAC 6/28/05</b>
	<b>CAC 7/25/06</b>
	<b>CAC 9/26/06</b>
	<b>CAC 9/25/07</b>
	<b>CAC 11/25/08</b>
	<b>CAC 11/24/09</b> Minor revision-medical necessity statement revised to state it applies to women with a singleton pregnancy.
	<b>CAC 11/30/10</b> Consensus Review
	<b>CAC 11/22/11</b> Minor Review. Policy statement revised to include use of vaginal progesterone to treat women with singleton pregnancies and short cervical length as medically necessary. Indication of short cervical length removed from investigational statement. Indications of cervical cerclage and uterine anomaly removed from medically necessary indications and added to investigational statement. Policy statement also revised to make start and stop dates of injectable progesterone consistent with FDA. "Not medically necessary" statement for home administration of progesterone suppositories deleted. FEP variation added. medically necessary. Indication of short cervical length removed from investigational statement. Indications of cervical cerclage and uterine anomaly removed from medically necessary indications and added to investigational statement. Policy statement also revised to make start and stop dates of injectable progesterone consistent with FDA. "Not medically necessary" statement for home administration of progesterone suppositories deleted. FEP variation added.

## MEDICAL POLICY



<b>POLICY TITLE</b>	<b>PROGESTERONE THERAPY AS A TECHNIQUE TO REDUCE PRETERM DELIVERY IN HIGH RISK PREGNANCIES</b>
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	<p><b>CAC 1/29/13</b> Minor. Investigational statement reformatted to bulleted list to improve readability. Added bullet point to investigational statement, “prior episode of preterm labor in current pregnancy (i.e. progesterone therapy in conjunction with tocolysis or following successful tocolysis).” For women with a singleton pregnancy and prior history of spontaneous preterm birth before 37 weeks’ gestation, the following may be considered medically necessary --- added the following statement as a medically necessary indication — “Daily vaginal progesterone between 24 and 34 weeks of gestation.</p> <p><b>CODES REVIEWED</b> 11/20/12 KLR</p>
	<p><b>CAC 1/28/14</b> Consensus. No change to policy statements. References updated. Rationale section added.</p>

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